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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/735,046	12/12/2003	Ilya Frolov	D6483	2564

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EXAMINER	
BURKHART, MICHAEL D	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/735,046	FROLOV ET AL.	
	Examiner	Art Unit	
	Michael D. Burkhart	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-14 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-14 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 12/12/2003 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

This application, filed 12/12/2003, claims priority benefit from provisional application 60/433,036, filed 12/12/2002.

Drawings

The drawings are objected to because "Helper" is misspelled as "Helperr" in Figures 13 and 14. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

Claims 1, 6, and 13 are objected to because of the following informalities: Claim 1 is missing the word "a" in line 3 (before the term "high titer") and line 20 (before the term "secondary stock"); Claims 6 and 13 are missing the word "the" before the term "replicational enhancer". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, and 8 recite the term "high titer(s)". Except for claims 7 and 14, which limit the low point of the titer, there is no further description of what values constitute a "high titer". Therefore, it is unclear what boundaries regarding viral titer are intended for the instant invention, and the metes and bounds of the claimed subject matter are indefinite. This rejection affects all dependent claims.

Claim 8 recites the term "large scale production" of a heterologous protein. There is no further description of what might constitute " large scale production ". Therefore, it is unclear what amounts of the heterologous protein are intended to be encompassed by the invention, and the metes and bounds of the claimed subject matter are indefinite. For example, purifying milligram quantities of a protein might be considered large scale production, but it is unclear if

purification of milligram quantities could be considered infringement of the instant claims. This rejection affects all dependent claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants claim a method to produce alphavirus particles by infecting a group of cells with an alphavirus stock prepared from the same group of cells Applicants disclose that Sindbis virus with nsP2 mutations (P726G and P726V) can be serially reproduced on BHK-21 cells. The claims read on a very large genus of potential alphaviruses and cell types. The written description requirement for a genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show that applicant was in possession of the claimed invention.

In the instant case, applicants only disclose the nsP2 mutations as prophetic examples of the claimed method. Neither applicants nor the prior art disclose that alphaviruses bearing these

mutations can be used in the method that is instantly claimed. Frolov et al (cited below, which describes the nsP2 mutations) show that infection by Sindbis virus replicons bearing these mutations is cytopathic (Table 1). Furthermore, applicants state (page 31, lines 3-7) that: "A spectrum of RNA replication efficiencies, ranging from 100% to 1% of the wild-type level, was observed in the BHK cells transfected by these mutants. Replicons with high levels of replication (> 30% of the wt level) could not persist in BHK cells and caused cell death within a few days." Given such a wide range of phenotypes from mutations at a single site, how can there be a basis for one skilled in the art to envision embodiments other than the disclosed mutations? Applicants claim the re-infection of cells by alphaviruses by function only, without a correlation between structure and function. The prior art does not compensate for the lack of description of specific examples of alphavirus mutants suitable as claimed. The lack of disclosure and broad genus regarding the claimed alphaviruses and cell types would require the skilled artisan to conclude that the example presented by the applicants are not sufficient to describe the claimed genus.

Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics,* Inc. 8 USPQD2d 1217 (Fed. Cir.

1988)). Whether undue experimentation is required is a conclusion reached by weighing several factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQQ2d 1400 (Fed. Cir. 1988) and include the following:

Unpredictability of the art. The art concerning infection of a group of cells with an alphaviral stock produced from said cells is unpredictable. Except in certain instances (mosquito cells, alphaviral mutants), alphaviral infection leads to a suppression of host macromolecular synthesis and cell death (Frolov et al., 1999). Therefore it is unpredictable that cells previously infected would still be viable, let alone that they could be productively re-infected with the same alphavirus. To circumvent this problem, Polo et al (1999) developed a mammalian cell line that transcribed alphaviral RNA in an inducible manner, thereby reducing viral RNA production and titer while allowing serial propagation of virus stocks. Frolov et al identify Sindbis virus mutants at position 726 in the nsP2 protein that display a wide range (wild-type to 1% of wild-type) of RNA replication efficiencies (Fig. 7B) and cytopathic effects (Table 1). Given this data, it is unpredictable that mutations at this single residue can lead to a Sindbis virus phenotype capable of serial replication in a mammalian cell. It is therefore equally unpredictable (or greater so) to prepare any alphavirus so that it can reproduce serially in any cell type.

State of the art. The state of the art regarding the infection of a group of cells with an alphaviral stock produced from said cells is poorly developed. The development of such viruses and cells would have to be done empirically.

Number of working examples. Applicants have provided no working examples of infection of a group of cells with an alphaviral stock produced from the same cells.

Amount of guidance. Applicants provide no direction for alphaviruses other than the nsP2 mutations (P726G and P726V) mentioned above that can be serially reproduced on any cell type. The specification requires the skilled artisan to practice trial and error experimentation with different alphaviruses, alphavirus mutants and cell lines to determine which (if any) will be compatible as claimed.

Scope of the invention. The claims are broad in nature and read on any alphavirus reproduced in any cell line from which the virus was produced.

Nature of the invention. The invention involves the unpredictable art infecting a group of cells with an alphaviral stock produced from said cells.

Level of skill in the art. While the level of skill in the art is high, the unpredictability of the art, lack of guidance, broad scope of the claims and poorly developed state of the art would require that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

Conclusion

No claims are allowed.

The closest prior art is exemplified by Smerdou et al (J. Virol., 1999). Smerdou et al teach the production of Semliki Forest virus (SFV) by transfection of BHK cells with a SFV replicon and two helper constructs expressing capsid and E1 separately. However, unlike the

instant application, they do not teach the modification of the 5' end of the constructs such that all are packaged into distinct alphavirus particles which are then used to infect host cells to amplify the alphavirus particles.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael D. Burkhart
Examiner
Art Unit 1636

DAVID GUZO
PRIMARY EXAMINER